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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,292	08/14/2006	Benny Bang-Andersen	463USPCT	3519

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EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,292	BANG-ANDERSEN ET AL.	
	Examiner	Art Unit	
	EMILY BERNHARDT	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 34-49 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 34-49 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 2/15/06&6/26/06&1/31/07&8/1/07& 1/16/08 & 2/12/08.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Scope of 'substantially pure" is not known. The extent of purity level being covered is not clear. 90%, 95%, 99% pure or some other numerical amount or range is possible but specification provides no guidance as to what degree of purity applicants intend to cover by these claims. While mention is made of varying degrees of purity for the term "stereochemically pure" such is not synonymous with the term recited in the claim.

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions having the compound of formula (I) along with pharmaceutically acceptable salts, does not reasonably provide enablement for any and all salts which are literally included within the claims' scope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Given the many salts which are solely used for preparative or industrial purposes which are included within the claim's scope, the rejection is believed proper. See for example Ex parte Reed 135 USPQ 34.

However, if applicants amend the claim 36 and/or claim 34 to recite pharmaceutically acceptable salts, it is not seen how this claim and 47 materially differ nor is it seen how 34 vs 46 and 38 vs 48 would materially differ. Applicants are requested to cancel duplicate claims resulting from any amendments to the claims.

Claims 38-45 and 48-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While being enabling for treating anxiety, depression, schizophrenia and psychotic disorders listed in the last paragraph on p.5 and 1st paragraph on p.6 of the specification does not reasonably provide enablement for treating remaining disorders or certain types of addiction particularly claimed in 45 and 49. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The notion that having combined affinity for the serotonin receptor (5-HT2A and D-1/D-2 receptors as well as α1 adrenoreceptors will enable

treatment of all sleep, abuse disorders,migraine, any disorder exhibiting psychotic symptoms as well as neurolpetic-induced parkinsonism is not substantiated by the current state of the art. Note Robichaud at best describes treating depression and anxiety for 5-HT 2A antagonists and Zhang on p.590 discusses dopamine antagonists for treating psychoses, in particular, schizophrenia. Also see Gonzalez-Gomez article dealing with piperazine derivatives having a similar profile of activity as urged herein where the discussion is directed to use as anti-psychotics. Note also the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition which considers factors such as:

1) Breadth of the claims- The claims cover (but are not limited to) to all types of sleep disorders which include many, many different types even diametric opposites, eg. narcolepsy vs sleep apnea, any and all disorders having psychotic symptoms which entails many different diseases of varying etiology, such as Alzheimer's Disease, Behcet's Disease, HIV-the latter for which it is known that anti-psychotic agents do not improve the psychotic symptoms. The scope of "abuse disorder" is not even a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates,

amphetamines, benzodiazepines, nicotine, etc all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine re-uptake site. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat chemical addictions generally have thus failed. While there are compounds undergoing preclinical and clinical trials for cocaine abuse that can block the behavioral effects of cocaine in animal models, there are no compounds that have proven efficacious in human cocaine addicts. See Newman, especially left column of p.1117 in the “Expert Opinion” section.

2) Level of skill in this art- as far as the examiner is aware drugs having the profile of activity relied on herein are not known for such a spectrum of clinical applications and thus the level of skill is low ;

3) State of the prior art- compounds similar in structure (note Bogeso references applied below) have not demonstrated such a range of uses- only *in vitro* affinity towards various receptors as herein;

4) Working examples- There are no test(s) directed to the many uses

pointed out above which are art-recognized for predicting *in vivo* efficacy in humans . Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of in vivo success for any additional diseases that may still be embraced in response to this action. See MPEP. 2164.05(a).

Thus in view of the above the rejection is being applied.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34,35 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Bogeso (J.Med.Chem). Bogeso describes the trans form of instant compound as a precursor for making 4-methylated analog as synopsized by applicants in the specification and described on p.4382 for making compound 38. The specification alternately refers to compound of

formula (I) being in the trans form or as an enantiomer. However the use of wedged and hatched bonds would suggest the trans isomer. Applicants should also note In re Adamson 125 USPQ 233 and the need for a purity limitation when claiming a particular stereoisomer.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bogeso (J.Med. Chem) and Bogeso (EP'073). While the instant trans-isomer is not taught for any medicinal uses in the J. Med. Chem article, the corresponding 4-methylated analog is. See compound 38 in Table 5 which is reported to have a profile of activity as herein . Note also that (-) and (+) isomers have been isolated. EP Bogeso teaches both compounds as interchangeable for the same uses claimed herein. See formula I on p.2 where R1 can be H or alkyl and Ar can be unsubstituted phenyl and 6-chloro can be present on the indan ring. Note Bogeso also includes the resolved isomers and particularly characterizes the invention as being directed to the trans- form. For a list of uses that overlap with that

claimed herein, see p.3. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify compound 38 in Bogeso including the resolved forms by substituting H for methyl on the piperazino nitrogen and in so doing obtain additional compound as the free base or salt form with the expectation that that such compounds will have the desired activity needed to practice the invention in view of the equivalency teachings outlined in EP Bogeso.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34-49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims directed to compounds, compositions and uses of copending Application No. 11/816394. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound claimed in the copending case has the same structure as herein. While the compound is further described by X-ray and other data, there is no evidence that the instant compound as the free base is different. Absent evidence to the contrary the provisional rejection will be maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 34-49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/816403 in view of EP Bogeso ('073). The compound in the copending case is directed to the malate salt of otherwise identical compound as that claimed herein. While said salt is not particularly described in the instant case, although fumarate and maleate salts are, Bogeso teaches the interchangeability of said salt forms with

malate. See p.4 which includes malic acid as one example of a pharmaceutically acceptable acid addition salt.

This is a provisional obviousness-type double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300).

Commonly assigned 11/816394 and 11/816403, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference

under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Copending case 10/568572 is further removed as it is methylated on piperazine nitrogen and solely directed to 2 types of salts, not particularly described in the present case.

Applicants' IDS filed 2/21/08 has several duplicate entries which were crossed out. However, Cox is not seen in the file. A copy is needed for consideration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Bernhardt/
Primary Examiner, Art Unit 1624

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